Antimicrobial Compounds from Endolichenic Fungi

Subjects: Biochemistry & Molecular Biology
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A lichen is a symbiotic relationship between a fungus and a photosynthetic organism, which is algae or cyanobacteria. Endolichenic fungi are a group of microfungi that resides asymptomatically within the thalli of lichens. Endolichenic fungi can be recognized as luxuriant metabolic artists that produce propitious bioactive secondary metabolites.

Keywords: endolichenic fungi ; antibacterial ; antifungal ; antiviral ; antiplasmodial ; secondary metabolites

1. Introduction

Thousands of microorganisms, including fungi and bacteria, often associate with living and dead plant tissues [1]. Oftentimes, the importance of these microorganisms is unobserved; only the saprotrophic and pathogenic relationships are being investigated, and are viewed as a troublesome group of organisms. However, there are groups of micro-organisms that are phyto-friendly and able to produce a plethora of secondary metabolites with significant biological activities that will aid them to adapt better to their surroundings [2][3].

Lichens are an amalgamation or a symbiotic partnership between a fungus and a photosynthetic organism. The heterotrophic fungal partner is termed as a “mycobiont”, while the photoautotrophic “photobiont”, could be either green algae or cyanobacteria [4][5][6]. As the mycobiont usually plays the more prominent member, lichens have traditionally exhibited characteristics similar to theirs. The two partners share water, nutrients and gases [6] and this mutualism allows the lichens to develop under extremely exceptional ecological conditions like deserts, rocky coasts, alpine zones and droughts [5][6][7][8]. Living under these unusual conditions enables lichens to give birth to a variety of luxurious compounds with complex structures and numerous bioactivities, making this a highly interesting stream for natural product chemists to pursue [8][9][10]. However, lichen flora is less abundant in the neighbourhood of urban and industrialized areas, as lichens are easily affected by air pollutants [11]. Lichens display a wide distribution of more than 20,000 different species worldwide [12], and have been utilized on various occasions in the past, such as in food, perfumes, dyes and as antidotes for folk medication [10][11].

2. Antimicrobial Compounds Extracted from Endolichenic Fungi

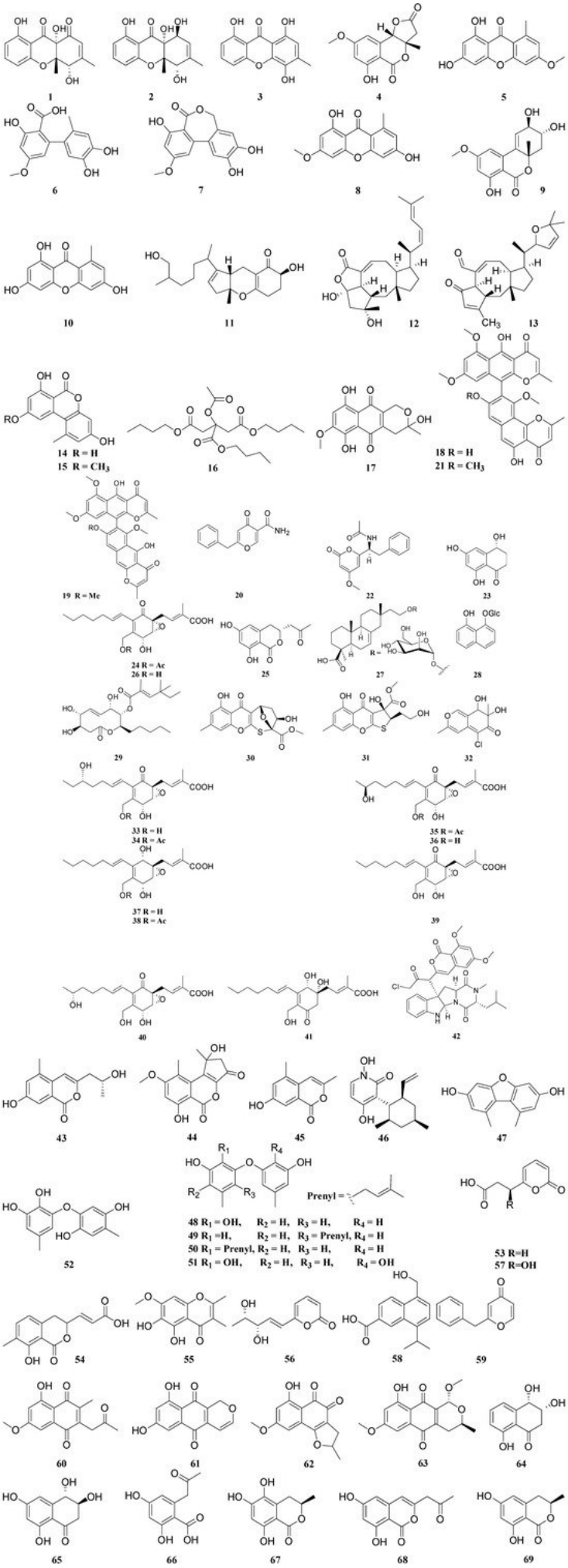
The need for new antimicrobial drugs is enhanced by the emergence of microbial resistance against almost all the currently available antibiotics and the sudden appearance of deadly viral infections [13]. Discovery of novel antimicrobial drugs was speculated as a solution to the growing threat of antibiotic-resistant microorganisms by the former secretary general of the United Nations, Ban Ki-Moon, at the UN General Assembly in 2016 [14].

The significant role of fungal species in producing antibiotics is elicited after the discovery of Penicillin G in 1928 [7]. Symbiotic fungal species like endophytic fungi are known to produce a plethora of antimicrobial compounds pertinent in therapeutics and agriculture [15]. Similar to other symbiotic fungi, ELF produces several secondary metabolites, which protect the lichen from biotic as well as abiotic stress [16]. ELF-derived antimicrobial compounds are one such group of metabolites essential to overcome the constant microbial threats faced by lichens. In some cases, extracts or natural products isolated from ELF show strong antimicrobial properties even though these bioactivities are not naturally observed within their ecological niche.

The discovery of many antimicrobial metabolites from ELF, establishes a hopeful satisfaction to the perpetual thirst for new antimicrobial drugs. However, these compounds might need further optimizations to modify their pharmacological and toxicological profiles. On the other hand, the development of synthetic pathways to produce these compounds, an industrial scale is essential to minimize the cost of production and minimize the environmental impacts. Thus, a detailed summary is provided here to describe the antimicrobial compounds isolated from ELF, including their sources, structures, activities and potencies in antimicrobial drug discovery.

Addressing the aforesaid requirement, **Table 1** of this review provides an overview of antimicrobial secondary metabolites isolated from ELF, which includes 31 antibacterial compounds, 58 antifungal compounds, two antiviral compounds, and one antiplasmodial (antimalarial) compound. The structures of these compounds are given in the **Figure 1**. Most of the authors have either reported only the antimicrobial properties of the lichenic and endolichenic fungal extracts without isolation of the metabolites responsible for the relevant bioactivity or have not quantified it in the form of Minimum Inhibitory Concentration (MIC) or IC_{50}. However, only the endolichenic fungal secondary metabolites, whose antimicrobial

properties are satisfactorily quantified, are summarized in this review. For ease of comparison, all of the antimicrobial potencies are presented in µg/mL and activities of the positive control are also given wherever available.



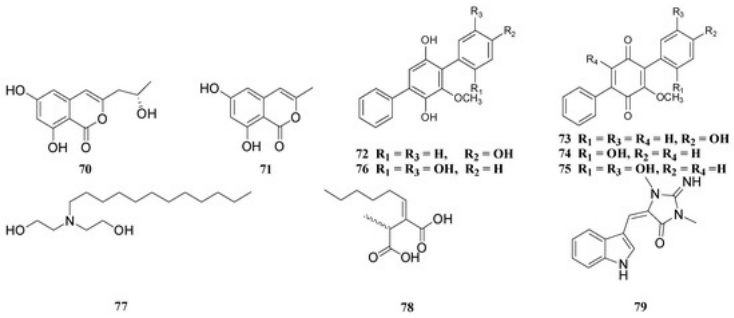


Figure 1. Structures of the antimicrobial compounds isolated from ELF.

Table 1. Antimicrobial Compounds Isolated from ELF.

Lichen	Endolichenic Fungi	No.	Compound	Microorganism	Activity (µg/mL)	Positive Control	Activity (µg/mL)	Ref
Diorygma hieroglyphicum	*Talaromyces funiculosus*	**1**	Funiculosone	*Escherichia coli*	IC_{50} = 25	-	-	
				Staphylococcus aureus	IC_{50} = 58	-	-	
		2	Mangrovamide J	*Escherichia coli*	IC_{50} = 65	-	-	
				Staphylococcus aureus	IC_{50} = 104	-	-	
		3	Ravenilin	*Escherichia coli*	IC_{50} = 23	-	-	
				Pseudomonas aeruginosa	IC_{50} = 96	-	-	
				Staphylococcus aureus	IC_{50} = 25	-	-	

Lichen	Endolichenic Fungi	No.	Compound	Microorganism	Activity (μg/mL)	Positive Control	Activity (μg/mL)	Ref
Everniastrum sp.	*Ulocladium* sp.	**4**	6-hydroxy-8-methoxy-3a-methyl-3a,9b-dihydro-3*H*-furo[3,2-c]isochromene-2,5-dione	*Bacillus subtilis*	IC_{50} = 25.0	Gentamicin	IC_{50} < 0.048	
		5	6-*O*-methylnorlichexanthone	*Bacillus subtilis*	IC_{50} = 0.39			
		6	Altenusin	*Bacillus subtilis*	IC_{50} = 11.3			
		7	Alterlactone	*Bacillus subtilis*	IC_{50} = 11.8			
		8	Griseoxanthone C	*Bacillus subtilis*	IC_{50} = 0.35			
		9	Isoaltenuene	*Bacillus subtilis*	IC_{50} = 14.7			
		10	Norlichexanthone	*Bacillus subtilis*	IC_{50} = 0.58			
				Methicillin Resistant *Staphylococcus aureus*.	IC_{50} = 5.4	Vancomycin	IC_{50} < 1.03	
		11	Tricycloalternarene 1b	Bacille Calmette-Guérin strain	MIC = 125	-	-	
	Ulocladium sp. (CHMCC 5507)	**12**	Ophiobolin P	*Bacillus subtilis*	MIC = 12.6	Gentamicin	MIC = 0.05	
				Methicillin Resistant *Staphylococcus aureus*.	MIC = 25.1	Vancomycin	MIC = 1.0	
		13	Ophiobolin T	Bacille Calmette-Guérin strain	MIC = 12.7	Hygromycin	MIC = 0.35	
				Bacillus subtilis	MIC = 6.3	Gentamicin	MIC = 0.05	
				Methicillin Resistant *Staphylococcus aureus*	MIC = 12.7	Vancomycin	MIC = 1.0	

Lichen	Endolichenic Fungi	No.	Compound	Microorganism	Activity (µg/mL)	Positive Control	Activity (µg/mL)	Ref
Parmelinella wallichiana	*Nigrospora sphaerica*	**14**	Alternariol	*Bacillus subtilis*	MIC = 31.2	Amikacin sulfate	MIC = 0.45	
				Escherichia coli	MIC = 62.5		MIC = 0.90	
				Staphylococcus aureus	MIC = 62.5		MIC = 0.90	
		15	Alternariol-9-methyl ether	*Bacillus subtilis*	MIC = 62.5		MIC = 0.45	
				Pseudomonas fluorescens	MIC = 31.2		MIC = 0.90	
				Staphylococcus aureus	MIC = 62.5		MIC = 0.90	
Parmotrema rampoddense	*Fusarium proliferatum*	**16**	Acetyl tributyl citrate	*Klebsiella pneumoniae*	MIC = 125	-	-	
				Pseudomonas aeruginosa	MIC = 125	-	-	
				Staphylococcus aureus	MIC = 125	-	-	
		17	Fusarubin	*Escherichia coli*	MIC = 1.56	-	-	
				Pseudomonas aeruginosa	MIC = 1.56	-	-	
				Staphylococcus aureus	MIC = 1.56	-	-	

Lichen	Endolichenic Fungi	No.	Compound	Microorganism	Activity (µg/mL)	Positive Control	Activity (µg/mL)	Ref
Parmotrema ravum	*Aspergillus niger*	**18**	Asperpyrone A	*Staphylococcus aureus* MTCC 737	IC_{50} = 112	-	-	
				Dickeya solani GBBC 1502	IC_{50} = 63	-	-	
				Listeria innocua LMG11387	IC_{50} = 141	-	-	
				Pectobacterium sp.	IC_{50} = 76	-	-	
		19	Aurasperone A	*Pseudomonas aeruginosa* MTCC 424	IC_{50} = 160	-	-	
				Pseudomonas syringae pv. Maculicola I11004	IC_{50} = 80	-	-	
				Staphylococcus aureus MTCC 737	IC_{50} = 135	-	-	
		20	Carbonarone A	*Dickeya solani* GBBC 1502	IC_{50} = 88	-	-	
		21	Fonsecinone A	*Escherichia coli* MTCC 443	IC_{50} = 47	-	-	
				Pseudomonas syringae pv. Maculicola I11004	IC_{50} = 154	-	-	
				Staphylococcus aureus MTCC 738	IC_{50} = 120	-	-	
		22	Pyrophen	*Aeromonas hydrophila* ATCC 7966	IC_{50} = 78	-	-	
				Listeria innocua LMG11387	IC_{50} = 86	-	-	
				Micrococcus luteus DPMB3	IC_{50} = 63	-	-	

Lichen	Endolichenic Fungi	No.	Compound	Microorganism	Activity (μg/mL)	Positive Control	Activity (μg/mL)	Ref
Sticta fuliginosa	*Xylariaceae* sp. (CR1546C)	**23**	(*R*)-4,6,8-trihydroxy-3,4-dihydro-1(2*H*)-naphthalenone	*Bacillus subtilis*	IC_{50} = 104.2	Streptomycin sulphate	IC_{50} = 5.2	
		24	18-*O*-acetylambuic acid	*Staphylococcus aureus* ATCC 6538	IC_{50} = 10.9	Antimicrobial peptide (AMP)		
		25	6,8-dihydroxy-(3*R*)-(2-oxopropyl)-3,4-dihydroisocoumarin	*Bacillus subtilis*	IC_{50} = 106.4	Streptomycin sulphate	IC_{50} = 5.2	
		26	Ambuic acid	*Staphylococcus aureus* ATCC 6538	IC_{50} = 15.4	Antimicrobial peptide (AMP)		
Usnea sp.	*Hypoxylon fuscum*	**27**	16-α-D-mannopyranosyloxyisopimar-7-en-19-oic acid	*Staphylococcus aureus* CGMCC 1.2465	MIC = 46.4	Vancomycin Hydrochloride	MIC = 3.12	
		28	8-methoxy-1-naphthyl-β-glucopyranoside	*Staphylococcus aureus* CGMCC 1.2465	MIC = 30.1			
		29	Phomol	*Staphylococcus aureus* CGMCC 1.2465	MIC = 21.1			
-	*Coniochaeta* sp.	**30**	Coniothienol A	*Enterococcus faecalis* (CGMCC 1.2535)	IC_{50} = 4.89	Ampicillin	IC_{50} = 2.61	
				Enterococcus faecium (CGMCC 1.2025)	IC_{50} = 2.00		IC_{50} = 0.51	
		31	Coniothiepinols A	*Enterococcus faecalis* (CGMCC 1.2535)	IC_{50} = 11.51		IC_{50} = 2.61	
				Enterococcus faecium (CGMCC 1.2025)	IC_{50} = 3.93		IC_{50} = 0.51	

Lichen	Endolichenic Fungi	No.	Compound	Microorganism	Activity (µg/mL)	Positive Control	Activity (µg/mL)	Ref
Cetraria islandica	*Myxotrichum* sp.	**32**	Myxodiol A	*Candida albicans* SC 5314	MIC = 128	Fluconazole	MIC = 2	
	Pestalotiopsis sp.	**33**	Ambuic acid derivative 1	*Fusarium oxysporum*	MIC = 8	Ketoconazole	MIC = 8	
		34	Ambuic acid derivative 2	*Fusarium oxysporum*	MIC = 32		MIC = 8	
		35	Ambuic acid derivative 4	*Verticillium dahlia*	MIC = 32		MIC = 1	
		36	Ambuic acid derivative 5	*Fusarium gramineum*	MIC = 8		MIC = 8	
				Fusarium oxysporum	MIC = 8		MIC = 8	
				Verticillium dahlia	MIC = 16		MIC = 1	
		37	Ambuic acid derivative 6	*Fusarium gramineum*	MIC = 8		MIC = 8	
		38	Ambuic acid derivative 7	*Rhizoctonia solani*	MIC = 32		MIC = 8	
		39	Ambuic acid derivative 8	*Rhizoctonia solani*	MIC = 32		MIC = 8	
		40	Ambuic acid derivative 9	*Fusarium gramineum*	MIC = 32		MIC = 8	
				Fusarium oxysporum	MIC = 16		MIC = 8	
		41	Ambuic acid derivative 11	*Fusarium gramineum*	MIC = 32		MIC = 8	
Cetrelia sp.	*Aspergillus* sp. CPCC 400810	**42**	Isocoumarindole A	*Candida albicans*	MIC = 32.0	Caspofungin	MIC = 0.03	
Diorygma hieroglyphicum	*Talaromyces funiculosus*	**1**	Funiculosone	*Candida albicans*	IC_{50} = 35	-	-	

Lichen	Endolichenic Fungi	No.	Compound	Microorganism	Activity (μg/mL)	Positive Control	Activity (μg/mL)	Ref
Everniastrum sp.	*Ulocladium* sp.	**43**	7-hydroxy-3-(2-hydroxy-propyl)-5-methyl-isochromen-1-one	*Candida albicans* SC 5314	IC_{50} = 45.4	Amphotericin B	IC_{50} = 1.03	
		44	7-hydroxy-3,5-dimethyl-isochromen-1-one	*Candida albicans* SC 5314	IC_{50} = 18.7			
		6	Altenusin	*Aspergillus fumigatus*	IC_{50} = 57.5		IC_{50} = 0.74	
		8	Griseoxanthone C	*Candida albicans* SC 5314	IC_{50} = 40.6		IC_{50} = 1.03	
		10	Norlichexanthone	*Aspergillus fumigatus*	IC_{50} = 43.6		IC_{50} = 0.74	
		45	Rubralactone	*Aspergillus fumigatus*	IC_{50} = 63.3		IC_{50} = 0.74	
				Candida albicans SC 5314	IC_{50} = 54.7		IC_{50} = 1.03	
Lethariella zahlbruckner	*Tolypocladium cylindrosporum*	**46**	Pyridoxatin	*Candida albicans* (Multiple strains)	MIC = 0.5 − 8.0	Fluconazole	MIC = 1.0 − 2.0	
				Candida glabrata (Multiple strains)	MIC = 1.0 − 8.0		MIC = 1.0 − 2.0	
				Candida krusei (Multiple strains)	MIC = 1.0 − 4.0		MIC = 1.0 − 2.0	
				Candida tropicalis CT2	MIC = 32		MIC = 2.0	

Lichen	Endolichenic Fungi	No.	Compound	Microorganism	Activity (µg/mL)	Positive Control	Activity (µg/mL)	Ref
Lobaria quercizans	*Aspergillus versicolor*	**47**	3,7-dihydroxy-1,9-dimethyldibenzofuran	*Candida albicans*	MIC = 64	Fluconazole	MIC = 2	
		48	Cordyol C	*Candida albicans*	MIC = 8			
		49	Diorcinol D	*Candida albicans*	MIC = 8			
		50	Diorcinol I	*Candida albicans*	MIC = 32			
		51	Violaceol I	*Candida albicans*	MIC = 8			
		52	Violaceol II	*Candida albicans*	MIC = 8			
Parmelia sp.	*Periconia* sp.	**53**	3-(2-oxo-2*H*-pyran-6-yl)propanoic acid	*Aspergillus niger*	MIC = 31	Cycloheximide	MIC < 16	
		54	Pericocin A	*Aspergillus niger*	MIC = 31	Cycloheximide	MIC < 16	
		55	Pericocin B	*Aspergillus niger*	MIC = 31			
		56	Pericocin C	*Aspergillus niger*	MIC = 31			
		57	Pericocin D	*Aspergillus niger*	MIC = 31			
		58	Pericoterpenoid A	*Aspergillus niger*	MIC = 31			
	Tolypocladium sp. (4259a)	**46**	Pyridoxatin	*Candida albicans*	MIC = 0.5	-	-	
Parmelinella wallichiana	*Nigrospora sphaerica*	**14**	Alternariol	*Candida albicans*	MIC = 80.0	Ketoconazole	MIC = 1.90	

Lichen	Endolichenic Fungi	No.	Compound	Microorganism	Activity (µg/mL)	Positive Control	Activity (µg/mL)	Ref
Parmotrema ravum	*Aspergillus niger*	**59**	Aspergyllone	*Candida parapsilosis*	IC_{50} = 52	-	-	
		19	Aurasperone A	*Candida krusei* MTCC 9215	IC_{50} = 373	-	-	
		20	Carbonarone A	*Candida albicans* MTCC 227	IC_{50} = 103	-	-	
				Candida krusei MTCC 9215	IC_{50} = 31	-	-	
		22	Pyrophen	*Candida albicans* MTCC 227	IC_{50} = 74	-	-	
				Candida glabrata	IC_{50} = 97	-	-	
				Candida utilis IHEM 400	IC_{50} = 62	-	-	
Pseudosyphellaria sp.	*Biatriospora* sp.	**60**	2-acetonyl-3-methyl-5-hydroxy-7-methoxynaphthazarin	*Candida albicans*	MIC = 64	Fluconazole	MIC = 2	
		61	6-deoxy-7-*O*-demethyl-3,4-anhydrofusarubin	*Candida albicans*	MIC = 32			
		62	Biatriosporin D	*Candida albicans*	MIC = 16			
		63	Biatriosporin K	*Candida albicans*	MIC = 64			

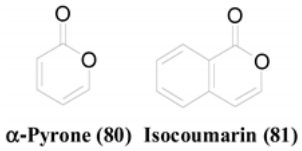
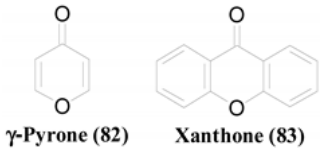
Lichen	Endolichenic Fungi	No.	Compound	Microorganism	Activity (μg/mL)	Positive Control	Activity (μg/mL)	Ref
Sticta fuliginosa	*Xylariaceae* sp. (CR1546C)	**64**	(3*R*,4*S*)-3,4,8-trihydroxy-3,4-dihydro-1(2*H*)-naphthalenone	*Candida albicans*	IC_{50} = 63.2	Amphotericin B	IC_{50} = 1.3	
		65	(3*S*,4*S*)-3,4,6,8-tetrahydroxy-3,4-dihydro-1(2*H*)-naphthalenone	*Candida albicans*	IC_{50} = 67.8			
		23	(*R*)-4,6,8-trihydroxy-3,4-dihydro-1(2*H*)-naphthalenone	*Candida albicans*	IC_{50} = 78.2			
		66	2,4-dihydroxy-6-(2-oxopropyl)-benzoic acid	*Candida albicans*	IC_{50} = 101.3			
		67	5,6,8-trihydroxy-3(*R*)-methyl-3,4-dihydroisocoumarin	*Candida albicans*	IC_{50} = 71.4			
		68	6,8-dihydroxy-(3)-(2-oxopropyl)-isocoumarin	*Candida albicans*	IC_{50} = 98.1			
		25	6,8-dihydroxy-(3*R*)-(2-oxopropyl)-3,4-dihydroisocoumarin	*Candida albicans*	IC_{50} = 71.2			
		69	6,8-dihydroxy-3(*R*)-methyl-3,4-dihydroisocoumarin	*Candida albicans*	IC_{50} = 65.1			
		70	6,8-dihydroxy-3-[(2*S*)-2-hydroxypropyl]-isocoumarin	*Candida albicans*	IC_{50} = 99.1			
		71	6,8-dihydroxy-3-methylisocoumarin	*Candida albicans*	IC_{50} = 67.2			
Umbilicaria sp.	*Floricola striata*	**72**	Floricolin A	*Candida albicans*	MIC = 16	-	-	
		73	Floricolin B	*Candida albicans*	MIC = 8	-	-	
		74	Floricolin C	*Candida albicans*	MIC = 8	-	-	
		75	Floricolin D	*Candida albicans*	MIC = 64	-	-	
		76	Terphenyl 2	*Candida albicans*	MIC = 64	-	-	

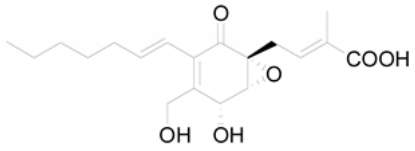
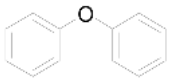
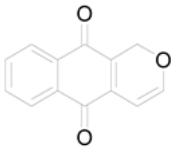
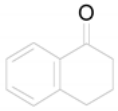
Lichen	Endolichenic Fungi	No.	Compound	Microorganism	Activity (µg/mL)	Positive Control	Activity (µg/mL)	Ref
Usnea baileyi	*Xylaria venustula*	**77**	*N*-dodecyldiethanolamine (DDE)	*Candida albicans* NCTC713	MIC = 5.5	-	-	[3]
		78	Piliformic acid	*Colletotrichum gloeosporioides*	MIC = 625.2	Captan	MIC = 5000	[3]
						Difenoconazole	MIC = 8.1	
-	*Coniochaeta* sp.	**31**	Coniothiepinols A	*Fusarium oxysporum* (CGMCC 3.2830)	IC_{50} = 13.12	Carbendazim	IC_{50} = 0.44	
Parmelinella wallichiana	*Nigrospora sphaerica*	**14**	Alternariol	Herpes Simplex Virus	IC_{50} = 34.9	-	-	
		15	Alternariol-9-methyl ether	Herpes Simplex Virus	IC_{50} = 64.0	-	-	
Usnea baileyi	*Xylaria venustula*	**79**	Isoplysin A	*Plasmodium falciparum*	MIC = 0.97	-	-	[3]

3. Structural Features Which Affect the Antimicrobial Activity of the Compounds

ELF are metabolically versatile organisms that can produce secondary metabolites belonging to different natural product classes. However, by observing the structures of the compounds isolated from ELF categorized above, some common scaffolds leading to distinct antimicrobial properties can be identified. Knowledge of the bioactivities of such chemical scaffolds plays an important role in rational drug discovery and in natural product-related research to make intelligent guesses about the potentials of isolated compounds. The presence of a large pool of data about the potencies of natural compounds or their synthetic or semi-synthetic derivatives with common scaffolds will be helpful in structure–activity relationship (SAR) studies. In order to facilitate such studies, we have summarized the structural scaffolds in **Table 2** that can be identified commonly among the antimicrobial compounds isolated from ELF.

Table 2. Common structural scaffolds among the antimicrobial compounds isolated from ELF.

Scaffold	Compounds
 α-Pyrone (80) Isocoumarin (81)	**4**, **9**, **14**, **15**, **25**, **42**, **43**, **44**, **45**, **53**, **54**, **56**, **57**, **66**, **67**, **68**, **69**, **70**, **71**
 γ-Pyrone (82) Xanthone (83)	**1**, **2**, **3**, **5**, **8**, **10**, **18**, **19**, **20**, **21**, **30**, **31**, **55**, **59**

Scaffold	Compounds
 Ambuic acid (26)	**24**, **26**, **33**, **34**, **35**, **36**, **37**, **38**, **39**, **40**, **41**
 Diphenyl ether (86)	**48**, **49**, **50**, **51**, **52**
 1*H*-Benzoisochromene-5,10-dione (84)	**17**, **61**, **63**
 3,4-Dihydro-2*H*-naphthalen-1-one (85)	**23**, **64**, **65**

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